Insights into the Role of Transient Chiral Mediators and Pyridone Ligands in Asymmetric Pd-Catalyzed C–H Functionalization

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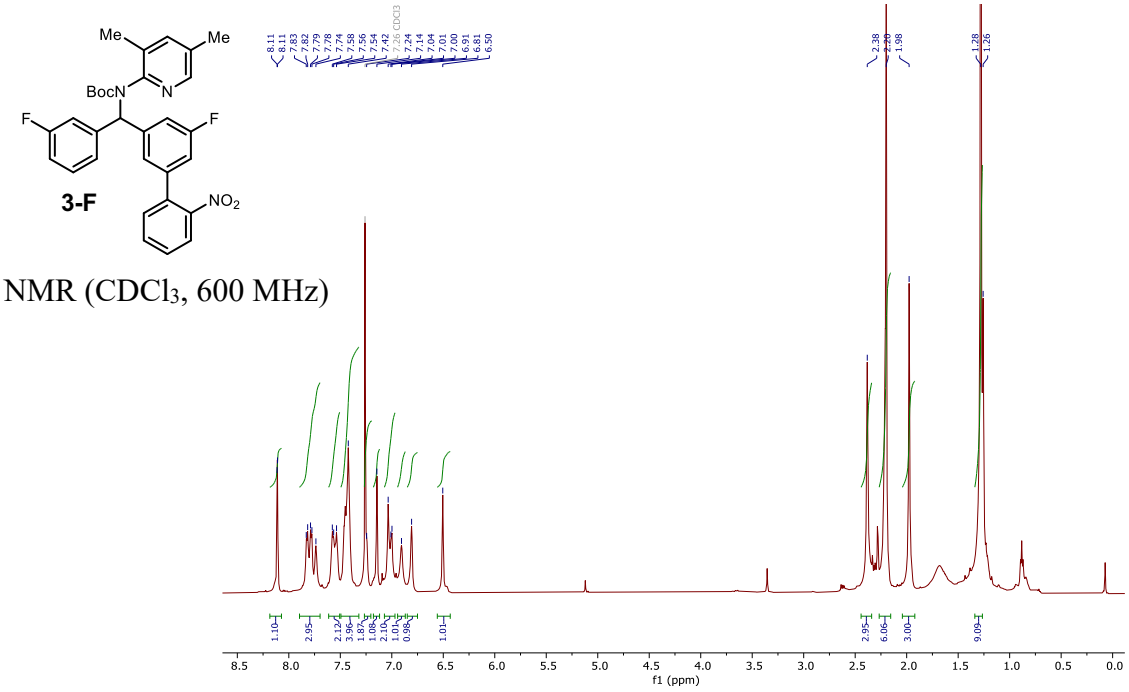
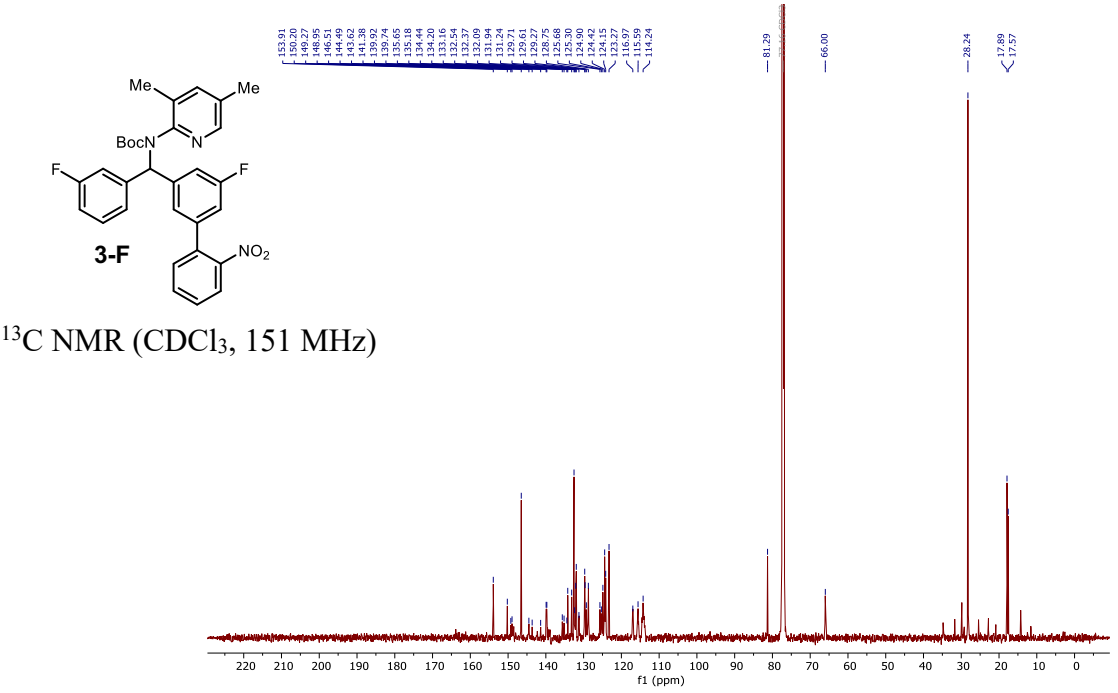
1 NMR Characterization Spectra



^{1}H NMR ($CDCl_3$, 600 MHz)

Figure S1 – ^{1}H NMR spectra of **3-F** in chloroform-*d*.



^{13}C NMR ($CDCl_3$, 151 MHz)

Figure S2 – ^{13}C NMR spectra of **3-F** in chloroform-*d*.

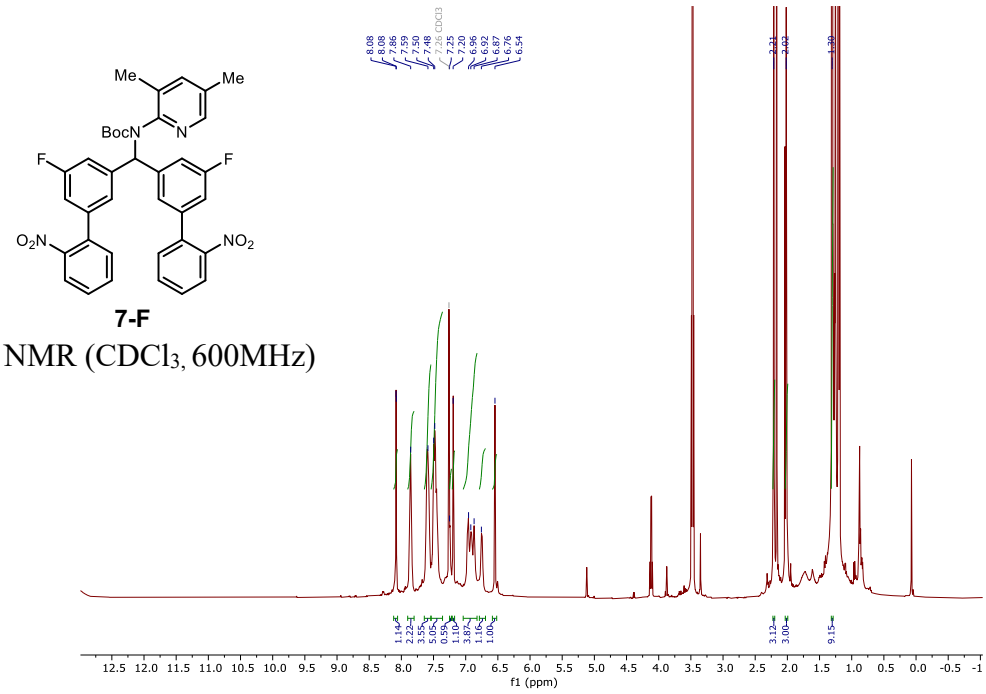


Figure S3 – ^{1}H NMR spectra of **7-F** in chloroform-*d*.

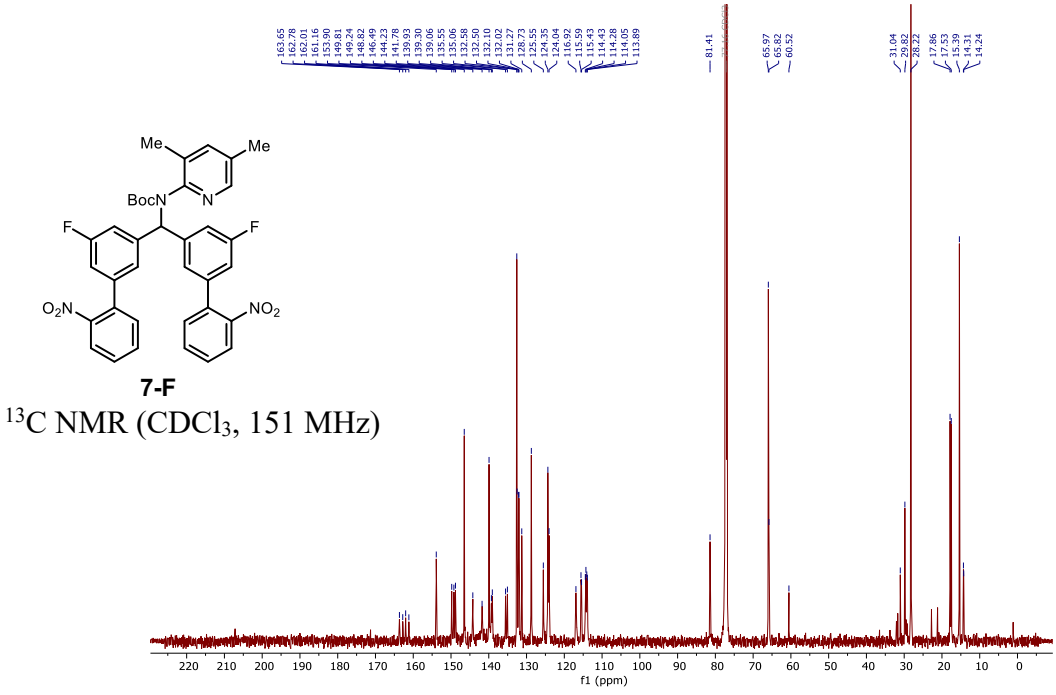


Figure S4 – ^{13}C NMR spectra of **7-F** in chloroform-*d*.

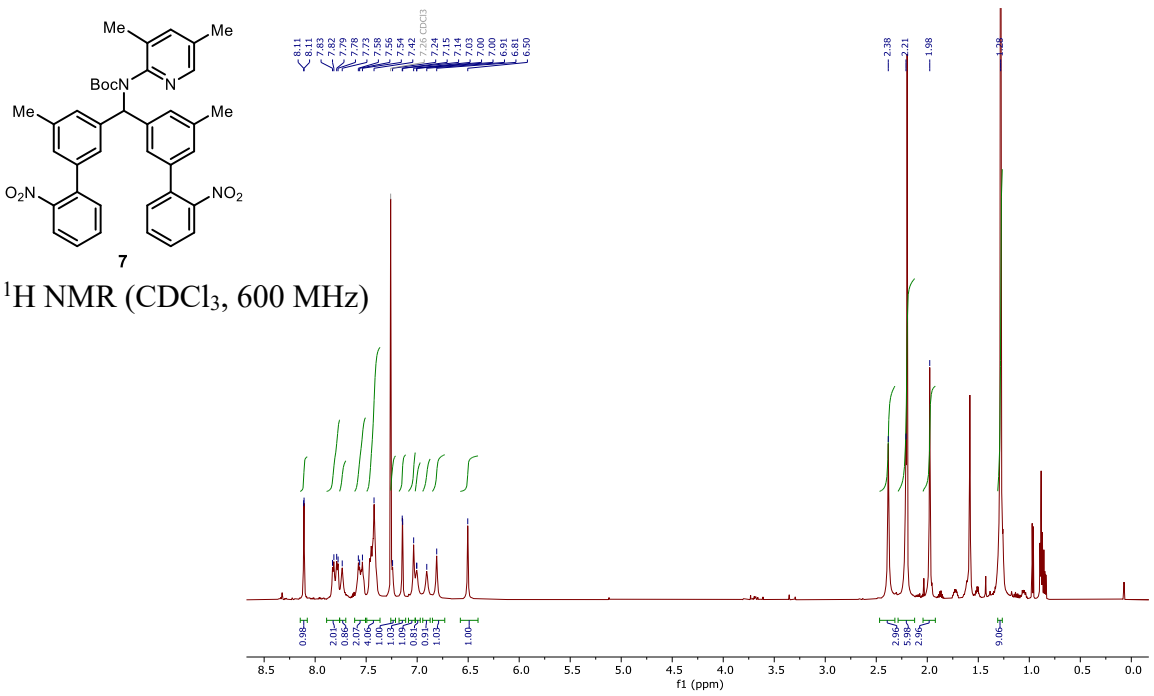


Figure S5 – ^{1}H NMR spectra of **7** in chloroform-*d*.

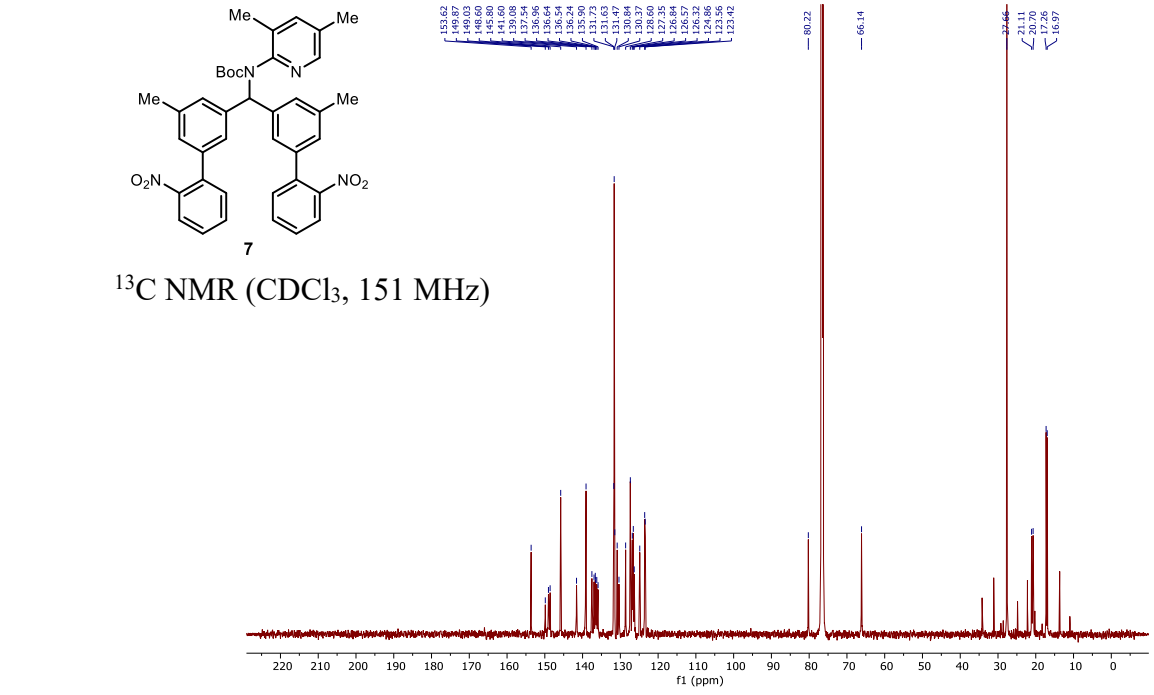


Figure S6 – ^{1}H NMR spectra of **7** in chloroform-*d*.

2 Kinetics

2.1 Kinetics Experiments at Same Excess

Experiments at same excess were designed using Reaction Progress Kinetic Analysis protocols[1-2] and were conducted as described by the general kinetics procedure except with the following changes designated in Table S1.

Experiment	[**1**] (M)	[**2**] (M)	AgOAc (mg)	Excess (M)
2.1.1	0.095	0.306	50.1	0.211
2.1.2	0.079	0.288	50.2	0.209

Table S1 – Conditions for 2.1.1 and 2.1.2: $[Pd(OAc)_2]$ = 0.01 M, [**4**] = 0.02 M, [**5**] = 0.015 M, and [decafluorobiphenyl] = 0.056 M. Excess is defined by Equation 1 in main paper.

2.2 Kinetics Experiments at Different Excess

Experiments at different excess were designed using Reaction Progress Kinetic Analysis protocols[1-2] and were conducted as described by the general kinetics procedure except with the following changes designated in Table S2.

Experiment	[**1**] (M)	[**2**] (M)	Ag_2CO_3 (mg)	Excess (M)
2.2.1	0.094	0.301	54.1	0.207
2.2.2	0.185	0.302	58.3	0.117
2.2.3	0.098	0.603	53.0	0.505

Table S2 – Conditions for 2.2.1, 2.2.2 and 2.2.3: $[Pd(OAc)_2]$ = 0.01 M, [**4**] = 0.02 M, [**5**] = 0.015 M, and [decafluorobiphenyl] = 0.053 M. Excess is defined by Equation 1 in main paper.

2.3 Kinetics Experiments Examining Rate Dependence on Diphenylphosphate (6)

Experiments aimed at interrogating the role of diphenylphosphate **6** in the reaction mechanism were conducted as described by the general kinetics procedure except with the following changes designated in Table S3.

Experiment	[**1**] (M)	[**2**] (M)	Ag_2CO_3 (mg)	[**6**] (M)
2.3.1	0.095	0.306	50.1	0
2.3.2	0.094	0.296	50.2	0.015

Table S3 – Conditions for 2.3.1and 2.3.2: $[Pd(OAc)_2]$ = 0.01 M, [**4**] = 0.02 M, [**5**] = 0.015 M, and [decafluorobiphenyl] = 0.056 M.

2.4 Kinetics Experiments Examining Rate Dependence on [4]

Experiments aimed at interrogating the reaction rate dependence on [**4**] were conducted as described by the general kinetics procedure except with the following changes designated in Table S4.

Experiment	[**1**] (M)	[**2**] (M)	Ag_2CO_3 (mg)	[**6**] (M)
2.4.1	0.091	0.333	42	0.02
2.4.2	0.091	0.334	40	0.04
2.4.3	0.088	0.317	41	0.01

Table S4 – Conditions for 2.4.1, 2.4.2, and 2.4.3: [$Pd(OAc)_2$] = 0.01 M, [**5**] = 0.015 M, and [decafluorobiphenyl] = 0.056 M. Total reaction volume is changed to 0.8 mL.

2.5 Kinetics Experiments Examining Rate Dependence on [Catalyst] and Associated Burés VTNA (Variable Time Normalization Analysis)[3]

Experiments were conducted as described by the general kinetics procedure except with the following changes designated in Table S5. The kinetic data from this experiment was processed using Burés VTNA analysis[3],and the results were listed in Tables S6, S7, and S8.

Experiment	[**1**] (M)	[**2**] (M)	[$Pd(OAc)_2$] (M)	Ag_2CO_3 (mg)
2.5.1	0.097	0.295	0.01	61
2.5.2	0.092	0.291	0.02	62
2.5.3	0.098	0.303	0.005	60

Table S5 – Conditions for 2.5.1, 2.5.2, and 2.5.3: [**5**] = 0.02 M, [**4**] = 0.02 M, and [decafluorobiphenyl] = 0.054 M. Total reaction volume is changed to 1.2 mL.

Time (min)	[**3**] based upon consumed [**1**] (M)	Time*[$Pd(OAc)_2$][1] (min*M)
2	0.000	0.02
30	0.005	0.3
60	0.011	0.6
93	0.017	0.93
120	0.022	1.2
180	0.032	1.8
240	0.041	2.4
365	0.055	3.65
475	0.065	4.75

Table S6 – Reaction progress data and VTNA analysis data for experiment 2.5.1.

Time (min)	[**3**] based upon consumed [**1**] (M)	Time*[$Pd(OAc)_2$]^1 (min*M)
2	0.000	0.044
15	0.010	0.33
30	0.017	0.66
45	0.023	0.99
60	0.028	1.32
93	0.038	2.046
120	0.044	2.64
180	0.057	3.96
240	0.068	5.28
365	0.084	8.03
475	0.090	10.45

Table S7 – Reaction progress data and VTNA analysis data for experiment 2.5.2.

Time (min)	[**3**] based upon consumed [**1**] (M)	Time*[$Pd(OAc)_2$]^1 (min*M)
2	0.000	0.011
30	0.003	0.165
60	0.007	0.33
93	0.010	0.5115
120	0.013	0.66
180	0.019	0.99
240	0.026	1.32
365	0.037	2.0075
475	0.046	2.6125

Table S8 – Reaction progress data and VTNA analysis data for experiment 2.5.3.

2.6 Kinetics Experiments Examining Rate Dependence on [5]

Experiments aimed at interrogating the reaction rate dependence on [**5**] were conducted as described by the general kinetics procedure except with the following changes designated in Table S9.

Experiment	[**1**] (M)	[**2**] (M)	Ag_2CO_3 (mg)	[**5**] (M)
2.6.1	0.095	0.302	63	0.01
2.6.2	0.094	0.306	54.1	0.016
2.6.3	0.097	0.295	61	0.020
2.6.4	0.101	0.296	57.2	0.033
2.6.5	0.098	0.301	52	0.0

Table S9 – Conditions for 2.6.1, 2.6.2, 2.6.3, 2.6.4, and 2.6.5: [$Pd(OAc)_2$] = 0.01 M, [**4**] = 0.02 M, and [decafluorobiphenyl] = 0.054 M. Total reaction volume is changed to 1.2 mL or 1.0 mL

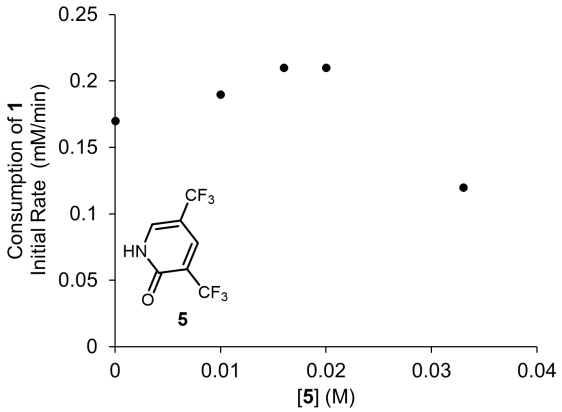


Figure S7 – Plot initial rate data for experiments from 2.6.

2.7 Temporal Monitoring of (±)-3 Degradation by Pd-(+)-4-5-Catalyzed C(aryl)–H Arylation

Experiments aimed at interrogating the degradation of (±)-**3** by Pd-(+)-**4**-**5**-Catalyzed C(aryl)–H Arylation were conducted as described by the general kinetics procedure except with the following changes designated in Table S10.

Experiment	[(±)-**3**] (M)	[(+)-**4**] (M)	Ag_2CO_3 (mg)
2.7	0.028	0.02	40

Table S10 – Conditions for 2.7: [$Pd(OAc)_2$] = 0.01 M, [**5**] = 0.015 M, and decafluorobiphenyl] = 0.01 M. Total reaction volume is changed 0.7 mL.

Time (min)	[(±)-**3**] (M)	[**7**] (M)	% *e.e.* of (*S*)-**3**
5	0.028	0.000	0
100	0.019	0.008	27
255	0.013	0.014	59
460	0.008	0.019	91

Table S11 – Temporal % *e.e.* of (*S*)-**3** for experiment 2.7.

2.8 Temporal Monitoring of (*S*)-3 Degradation by Pd-(±)-4-5-Catalyzed C(aryl)–H Arylation

Experiments aimed at interrogating the degradation of (*S*)-**3** by Pd-(±)-**4**-**5**-Catalyzed C(aryl)–H Arylation were conducted as described by the general kinetics procedure except with the following changes designated in Table S12.

Experiment	[(*S*)-**3**] (M)	[(±)-**4**] (M)	Ag_2CO_3 (mg)
2.8	0.019	0.02	42

Table S12 – Conditions for 2.8: [$Pd(OAc)_2$] = 0.01 M, [5] = 0.015 M, and decafluorobiphenyl] = 0.01 M. Total reaction volume is changed 0.7 mL.

Time (min)	[**3**] (M)	[**7**] (M)	% *e.e.* of (*S*)-**3**
5	0.019	0.000	92
100	0.013	0.005	91
255	0.008	0.012	91
460	0.002	0.016	98

Table S13 – Temporal % *e.e.* of (*S*)-**3** for experiment 2.8

2.9 Temporal Monitoring of Reaction Enantioselectivity in the Presence and Absence of 6

Experiments aimed at interrogating the rate dependence on [**6**] were conducted as described by the general kinetics procedure except with the following changes designated in Table S14.

Experiment	[**1**] (M)	[**2**] (M)	Ag_2CO_3 (mg)	[**6**] (M)
2.9.1	0.095	0.306	50.1	0.015
2.9.2	0.094	0.296	50.2	0

Table S14 – Conditions for experiments 2.9.1 and 2.9.2: $[Pd(OAc)_2]$ = 0.01 M, [(+)-**4**] = 0.02 M, [**5**] = 0.015 M, [decafluorobiphenyl] = 0.056 M, reaction temperature = 81 °C with a total reaction volume = 1.0 mL

3 Nonlinear Effect Measurements

Experiments were conducted as described by the general kinetics procedure except with the following changes described in Table S15.

Experiment	% *e.e.* of **4**	% Conversion of **1**	% *e.e.* of **3**	Ag_2CO_3 (mg)
3.1	0	28	0	51.5
3.2	20	30	17	53.
3.3	40	32	33	50.
3.4	60	28	46	50.
3.5	80	31	66	53.
3.6	100	32	84	51.

Table S15 – Conditions for nonlinear effect experiments: $[Pd(OAc)_2]$ = 0.01 M, [**4**] = 0.02 M, [**5**] = 0.015 M, [**1**] = 0.095, [**2**] =0.31 M, [**6**] = 0.015 M, and [decafluorobiphenyl] = 0.054 M. Total reaction volume is 1.0 mL. Reactions were quenched with ethyl acetate and chromatographed to isolate **3.**

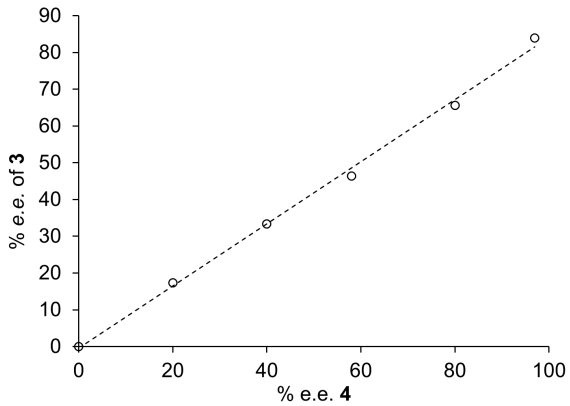


Figure S8 – Plot of nonlinear effect measurements from experiments 3.1 thru 3.6.

4 ^{19}F NMR Spectroscopy

4.1 *In-Situ* ^{19}F NMR Reaction Monitoring of the Reaction in Figure 7 in main paper

4.1.1 ^{19}F NMR study for the Reaction in Figure 7A in the main paper

Palladium acetate (18.4 mg, 0.082 mmol) was added to a 2 mL volumetric flask and dissolved in chloroform-d_1 using sonication to prepare a palladium solution ([$Pd(OAc)_2$] = 0.041 M). (+)-**4** (12.3 mg, 0.081 mmol), **5** (14.5 mg, 0.063 mmol), and decafluorobiphenyl (6.7 mg, 0.020 mmol) were added to a 1 mL volumetric flask and dissolved in chloroform-d_1 using sonication to prepare a (+)-**4**/**5**/decafluorobiphenyl solution ([(+)-**4**] = 0.081 M, [**5**] = 0.063 M, [decafluorobiphenyl] = 0.02 M).

To a NMR tube was added **2** (18.7 mg, 0.082 mmol), **1-F** (11. mg, 0.026 mmol), silver acetate (26. mg, 0.15 mmol), palladium stock solution (250 µL), and (+)-**4**/**5**/ decafluorobiphenyl stock solution (250 µL). The NMR was sealed with a screw cap and placed in a NMR spectrometer heated to 50 °C. ^{19}F NMR spectra were acquired every 30 minutes over the course of 12 hours and referenced to decafluorobiphenyl.

4.1.2 ^{19}F NMR study for the Reaction in Figure 7B in the main paper

Palladium acetate (11.3 mg, 0.05 mmol) and decafluorobiphenyl (6.8 mg, 0.02 mmol) were added to a 1 mL volumetric flask and dissolved in chloroform-d_1 using sonication to prepare a palladium/decafluorobiphenyl solution ([$Pd(OAc)_2$] = 0.05 M, [decafluorobiphenyl] = 0.02 M). (+)-**4** (15.1 mg, 0.01 mmol) was added to a 1 mL volumetric flask and dissolved in chloroform-d_1 using sonication to prepare a (+)-**4** stock solution ([(+)-**4**] = 0.10 M).

To a NMR tube was added **2** (17.5 mg, 0.076 mmol), **1-F** (10.8 mg, 0.025 mmol), silver acetate (25.5 mg, 0.15 mmol), palladium/decafluorobiphneyl stock solution (250 µL), and (+)-**4** stock solution (250 µL). The NMR was sealed with a screw cap and placed in a NMR spectrometer heated to 50 °C. ^{19}F NMR spectra were acquired every 30 minutes over the course of 12 hours and referenced to decafluorobiphenyl.

4.1.3 ^{19}F NMR study for the Reaction in Figure 7C in the main paper

Palladium acetate (26.7 mg, 0.120 mmol) was added to a 3 mL volumetric flask and dissolved in chloroform-d_1 using sonication to prepare a palladium solution ([$Pd(OAc)_2$] = 0.040 M).

To a NMR tube was added **1-F** (8.5 mg, 0.020 mmol), silver acetate (25. mg, 0.15 mmol), palladium stock solution (500 µL), and decafluorobiphenyl (1.7 mg, 0.005 mmol). The NMR was sealed with a screw cap and placed in a NMR spectrometer heated to 50 °C. ^{19}F NMR spectra were acquired every 30 minutes over the course of 12 hours and referenced to decafluorobiphenyl.

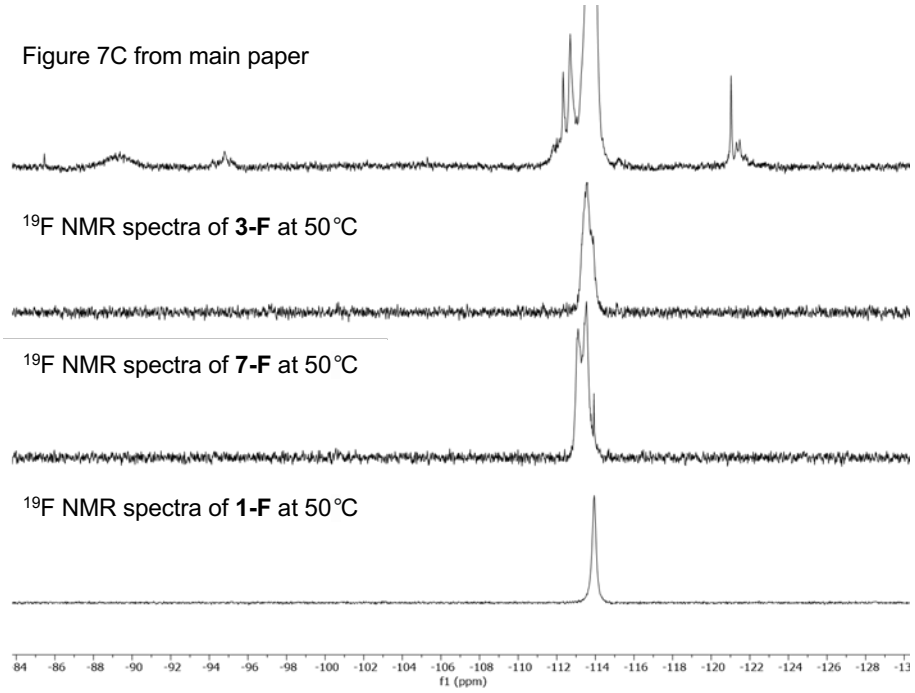


Figure S9 – ^{19}F NMR spectra of experiment 4.1.1, **3-F** at 50 °C, **7-F** at 50 °C, and **1-F** at 50 °C.

5 RP-HPLC with DAD Detection

The chromatographic separation was accomplished on a Waters I-Class LC with a Waters CORTECS C18 column (1.6 µm, 2.1x55 mm) using a 0.1% aqueous formic acid:acetonitrile gradient (0.8 mL/min, 30-99% acetonitrile over 2.9 minutes) at 55 °C. The products were detected by UV light (225 nm).

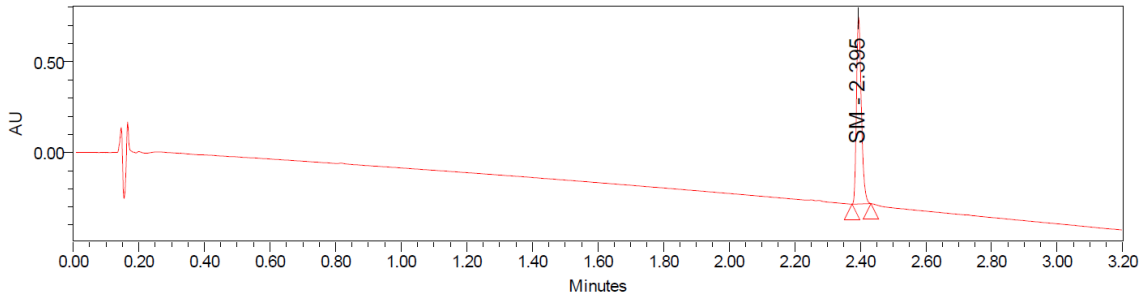


Figure S10 – RP-HPLC of **1**

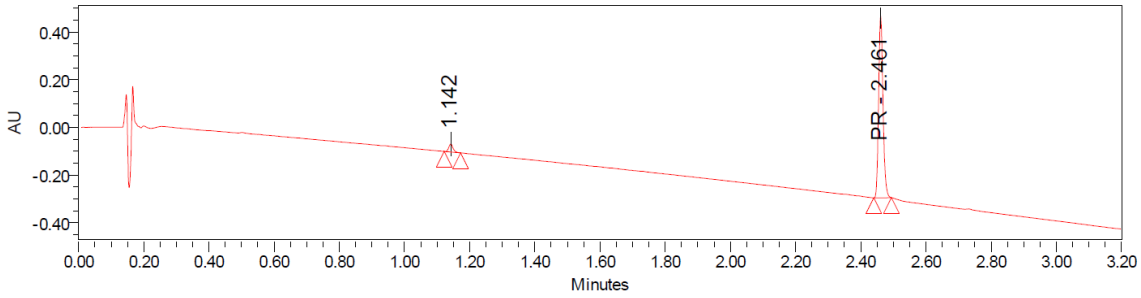


Figure S11 – RP-HPLC of **3**

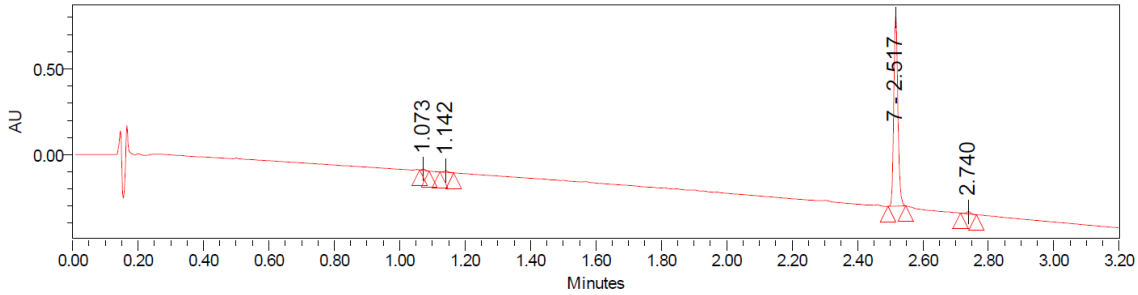


Figure S12 – RP-HPLC of **7**

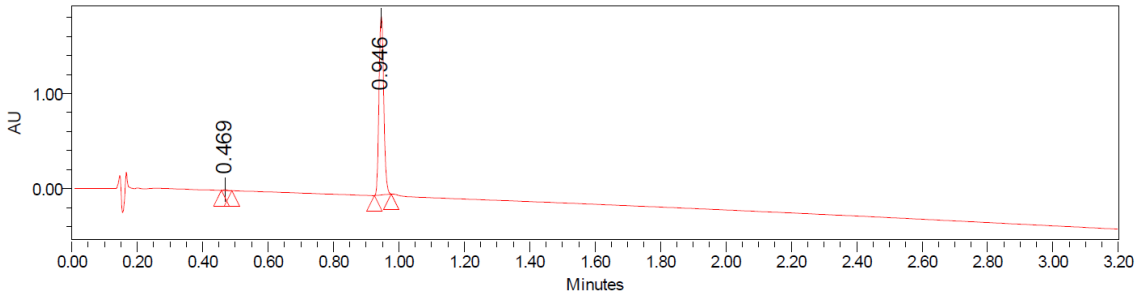


Figure S13 – RP-HPLC of **2**

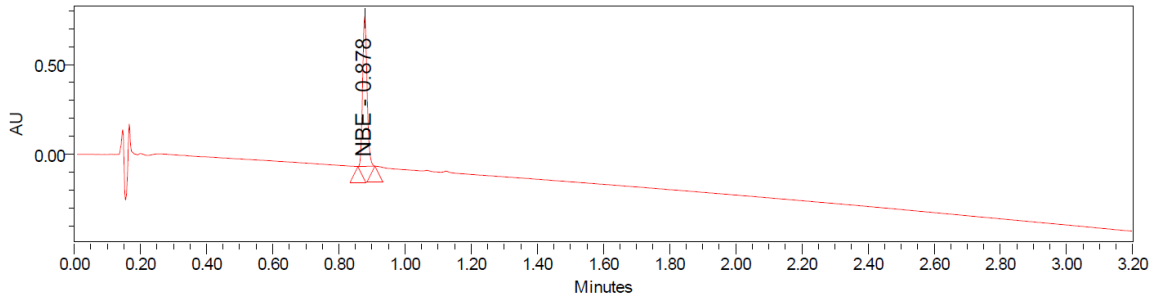


Figure S14 – RP-HPLC of **4**

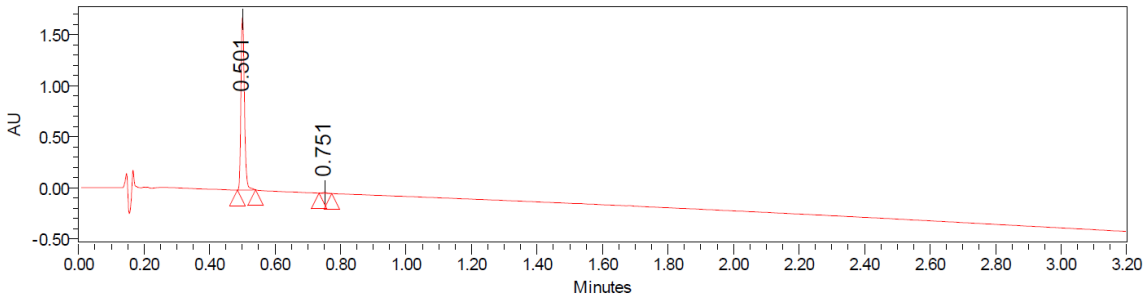


Figure S15 – RP-HPLC of **5**

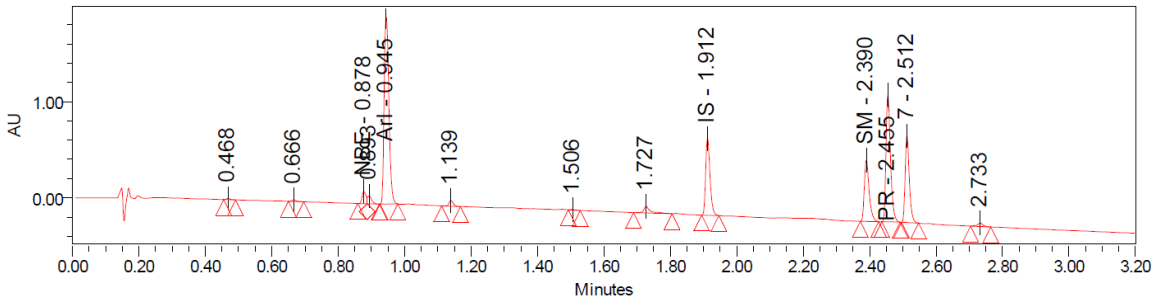


Figure S16 – RP-HPLC of crude reaction mixture for a reaction from Scheme 2 of main paper.

6 Normal Phase HPLC on Chiral Stationary Phase

The enantiomeric excess of **3** was analyzed by normal phase HPLC with Chiralcel OD-H column (5 mμ, 4.6 x 250 mm) under isocratic conditions [97% hexanes / 3% isopropanol, 1.0 mL/min] at 25 °C. The enantiomers were detected by UV light (210 nm).

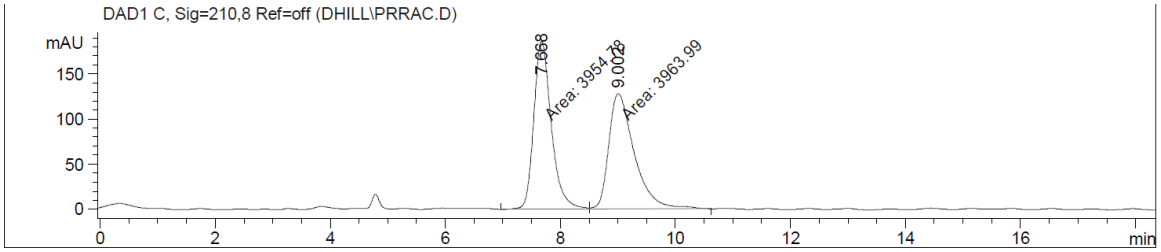


Figure S17 –Normal phase HPLC on chiral stationary of (±)-**3**.

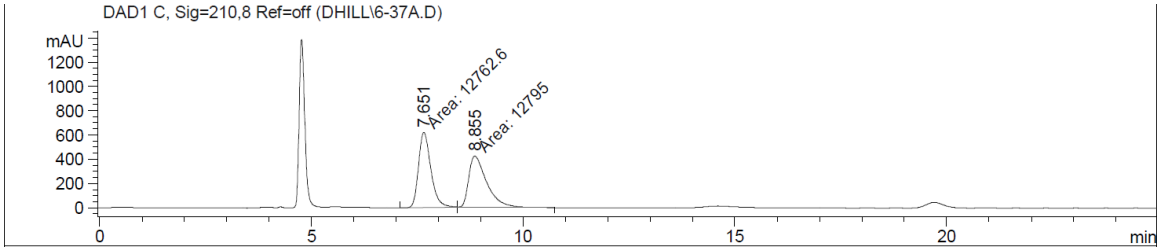


Figure S18 – Normal phase HPLC on chiral stationary of **3** from experiment 3.1.

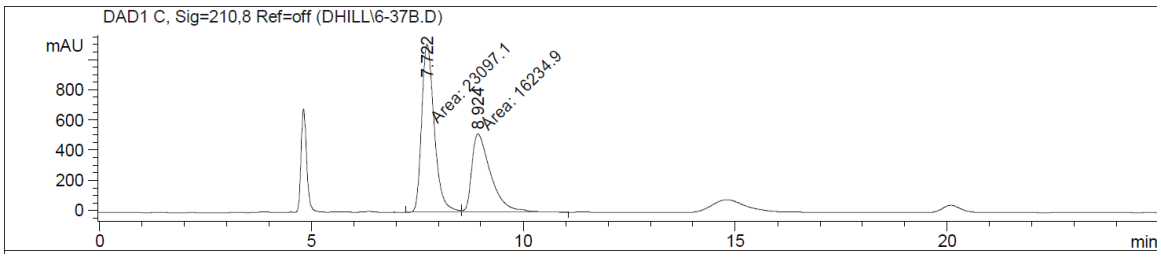


Figure S19 – Normal phase HPLC on chiral stationary of **3** from experiment 3.2

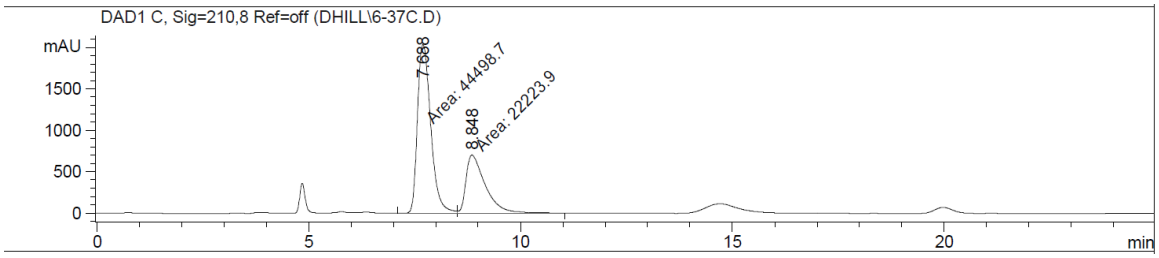


Figure S20 – Normal phase HPLC on chiral stationary of **3** from experiment 3.3

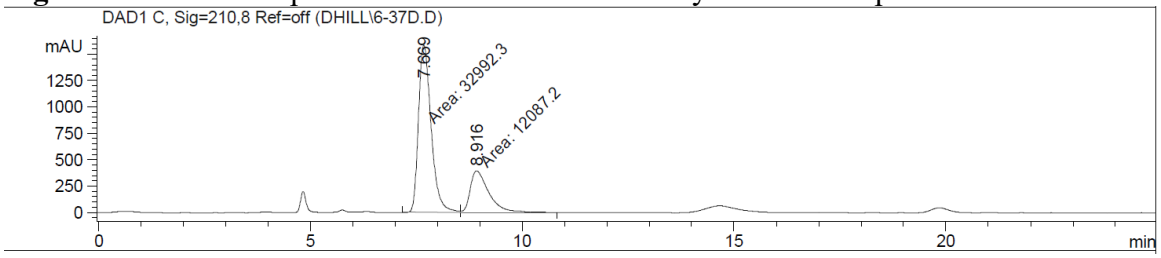


Figure S21 – Normal phase HPLC on chiral stationary of **3** from experiment 3.4.

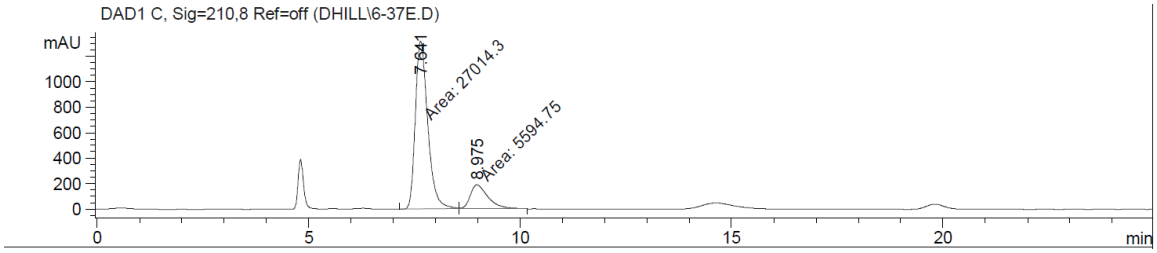


Figure S22 – Normal phase HPLC on chiral stationary, **3** from experiment 3.5.

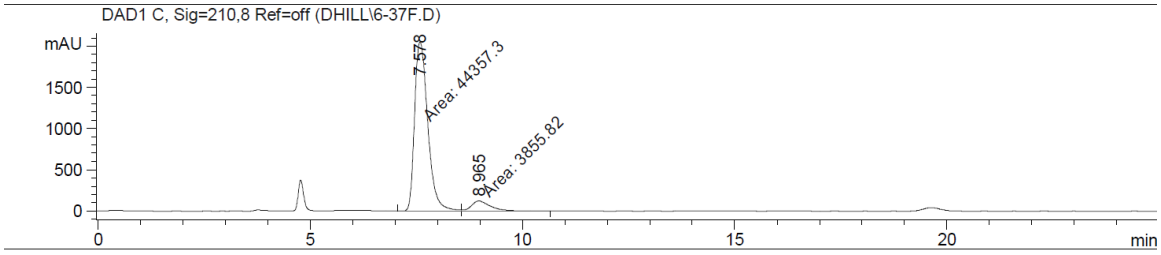


Figure S23 – Normal phase HPLC on chiral stationary, **3** from experiment 3.6.

7 2D-RP-LC-SFC Measurements

The enantiomeric excess was determined by heart-cutting 2D LC-SFC.[4] The LC dimension consisted of a Waters I-Class LC with a Waters BEH C18 column (1.7 µm, 2.1x100 mm) using a 0.1% aqueous formic acid:acetonitrile gradient (0.6 mL/min, 15-99% acetonitrile over 2.1 minutes) at 55 °C. The heart cut was performed at 2.46 minutes using a 6-port 2-position valve equipped with a 10 mL transfer loop. The SFC dimension consisted of a Waters UPC2 SFC with a Daicel IB column (3 µm, 4.6x250 mm) using isocratic conditions (4 mL/min, 10% IPA / CO2, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (214 nm).

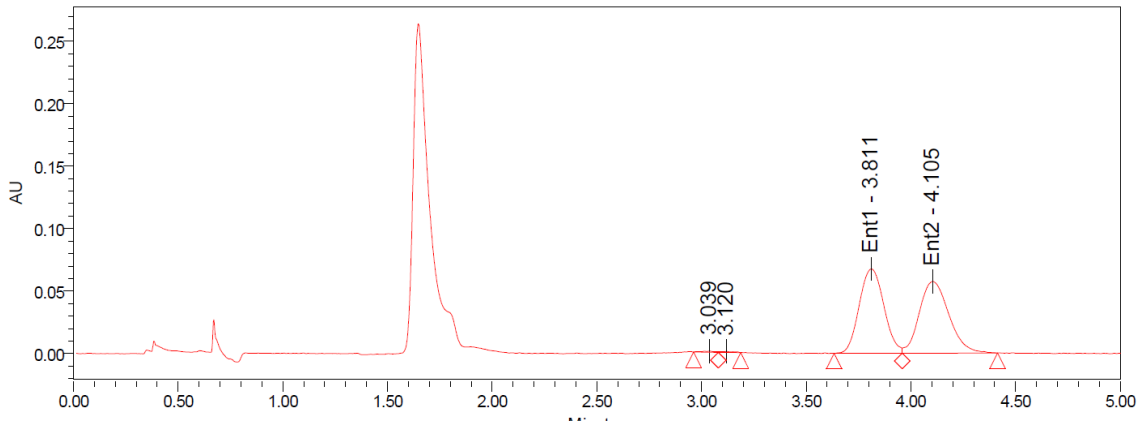


Figure S24 – RP-LCSFC of (±)-**3**.

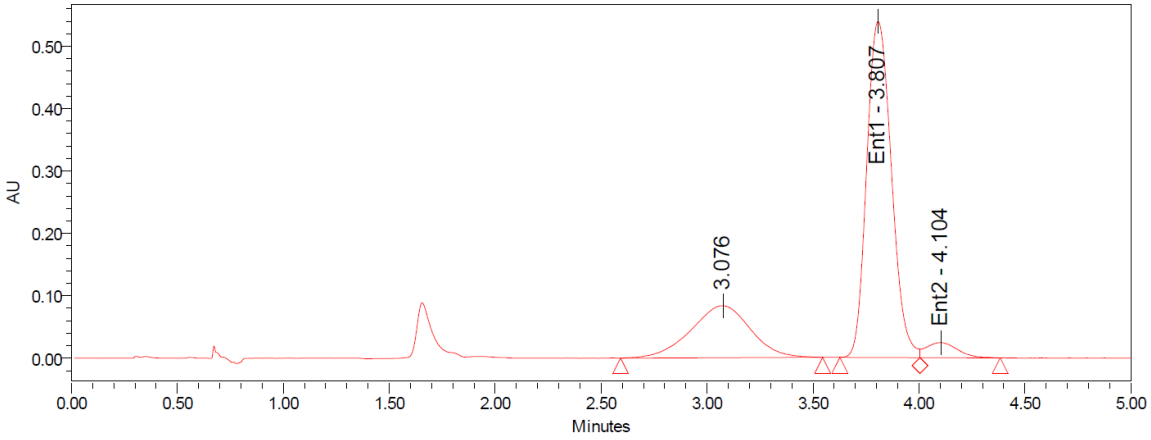


Figure S25 – RP-LCSFC of enantioenriched (+)-**3**.

8 References

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